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Chapter 21: Cirrhosis and Portal Hypertension

INTRODUCTION

- *Definition:* Cirrhosis is characterized by chronic liver injury, resulting in the development of regenerative nodules surrounded by dense fibrotic material, which leads to changes in splanchnic vasculature and circulation with gastroesophageal varices and bleeding, ascites, portal hypertension, encephalopathy, and coagulation disorders. Portal hypertension is characterized by hypervolemia, increased cardiac index, hypotension, and decreased systemic vascular resistance. Ascites is the pathologic accumulation of fluid within the abdomen. It is a common complication of cirrhosis.
- Primary causes of cirrhosis in developed countries include hepatitis C, excessive alcohol intake, and nonalcoholic fatty liver disease (**Table 21-1**).
- Hepatic encephalopathy (HE) is a functional disturbance of the brain caused by liver insufficiency or portal systemic shunting that presents on a spectrum of symptom severity ranging from subclinical alterations to coma.

TABLE 21-1

Etiology of Cirrhosis

Alcohol use disorder
Chronic hepatitis C
Metabolic liver disease Hemochromatosis Wilson's disease Steatotic liver disease metabolic dysfunction–associated steatohepatitis
Immunologic disease Autoimmune hepatitis Primary biliary cirrhosis Primary biliary cholangitis
Vascular disease Budd–Chiari
Drug-induced liver injury (below list not all-inclusive) Isoniazid, macrolides, amoxicillin-clavulanate, nitrofurantoin, fluoroquinolones, amiodarone, nonsteroidal anti-inflammatory drugs, allopurinol, sulfasalazine, methotrexate, interferon-β, interferon-α, anti-tumor necrosis factor inhibitors, valproate, lamotrigine, phenytoin, carbamazepine, green tea extract

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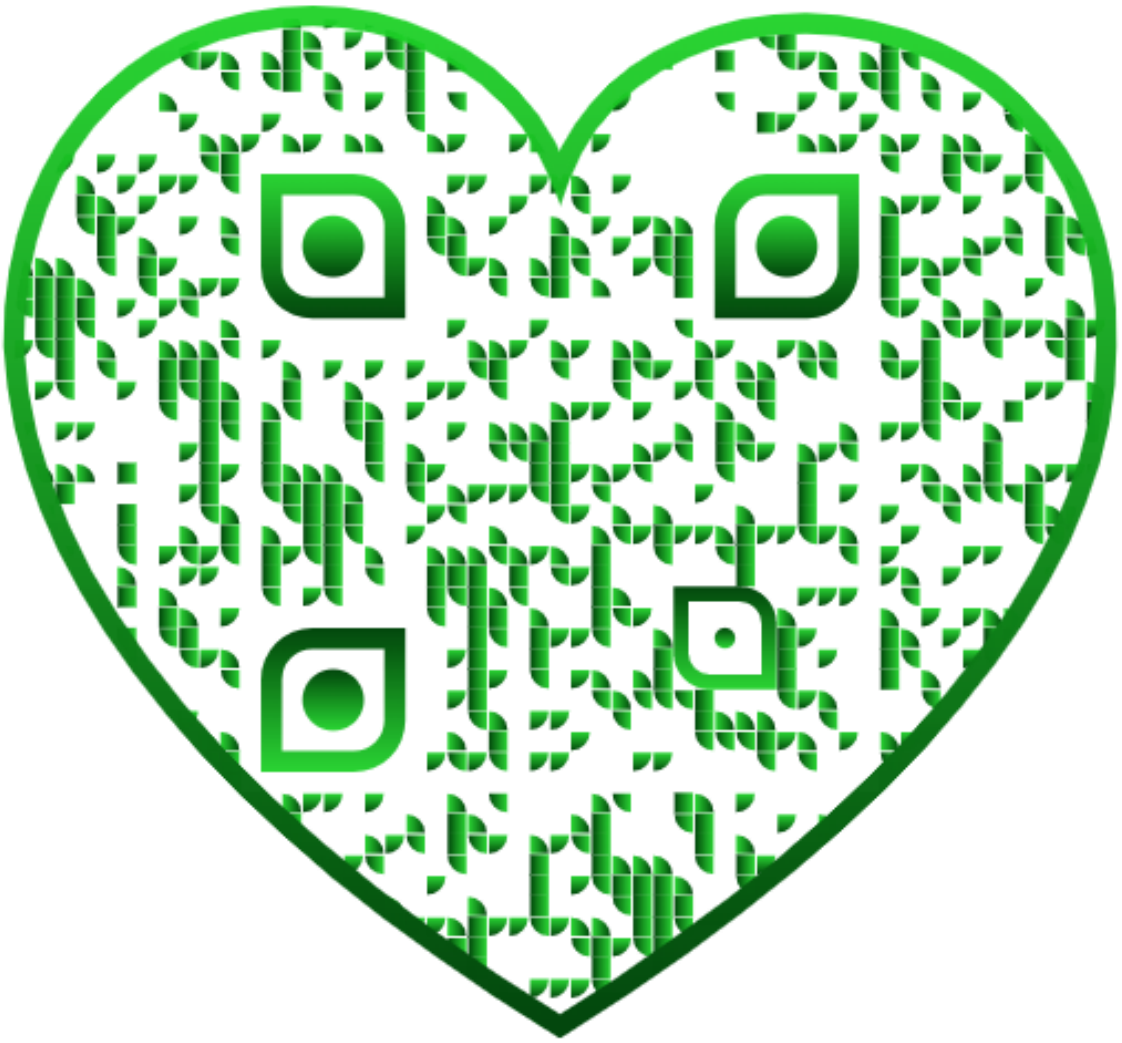

CLINICAL PRESENTATION

- Initial symptoms of cirrhosis may be nonspecific, including muscle cramps, fatigue, loss of appetite, and weight loss (**Table 21-2**). Patients may also present with much more significant symptoms secondary to decompensation related to cirrhosis complications such as ascites (abdominal distention) and HE (confusion, lethargy).
- Muscle wasting, palmar erythema, spider angiomas, parotid gland enlargement, white nails, Dupuytren contracture, asterixis, and metabolic complications including gynecomastia, testicular atrophy, and axillary hair loss are all possibly related to cirrhosis.
- A thorough history including risk factors that predispose patients to cirrhosis or nonalcoholic liver disease should be taken. Diagnostics for cirrhosis include liver function tests, coagulation tests, complete blood count, and serologic tests for viral causes, including hepatitis B and C.
- Portal hypertension is defined by the presence of a gradient of >5 mm Hg (0.7 kPa) between the portal and central venous pressures. Progression to bleeding can be predicted by Child–Pugh score, size of varices, and the presence of red wale markings on the varices. First variceal hemorrhage occurs at an annual rate of about 15% and carries a mortality of 7%–15%.
- The symptoms of HE include a wide spectrum of symptom severity ranging from subclinical alterations to coma that are thought to result from an accumulation of gut-derived nitrogenous substances in the systemic circulation. These substances then enter the central nervous system (CNS) and result in alterations of neurotransmission that affect consciousness and behavior.
- End-stage chronic liver disease is associated with decreased levels of most procoagulant factors, while two procoagulant factors, factor VIII and von Willebrand factor, are actually elevated, resulting in thrombosis or clinically significant bleeding.
- Thrombocytopenia, a common finding in cirrhosis, could promote bleeding.

TABLE 21-2

Clinical Presentation of Cirrhosis

Signs and Symptoms • Asymptomatic • Muscle cramps • Anorexia, weight loss • Splenomegaly • Jaundice, palmar erythema, and spider nevi • Gynecomastia, sexual dysfunction • Ascites and edema • Malaise, anorexia, and weight loss • Encephalopathy
Laboratory Tests • Hypoalbuminemia • Elevated prothrombin time (PT) • Thrombocytopenia • Elevated alkaline phosphatase • Elevated aspartate transaminase (AST), alanine transaminase (ALT), and γ-glutamyl transpeptidase (GGT)

LABORATORY ABNORMALITIES

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- Testing may include an antinuclear antibody titer to evaluate for the presence of autoimmune hepatitis; serum iron and transferrin saturation, possibly in conjunction with genetic testing, to look for hemochromatosis; and alpha-1 antitrypsin level and genotyping to test for alpha-1 antitrypsin deficiency, a rare disease, but one that can lead to liver and lung disease.
- The aminotransferases, AST and ALT, are enzymes that have increased concentrations in plasma after acute or chronic hepatocellular injury. The highest elevations (>10,000 units per liter [167 μkat/L]) are most likely to occur in shock liver and drug- or toxin-induced hepatitis. The ratio of AST to ALT with AST>ALT is more likely when cirrhosis of any etiology exists but also occurs in alcoholic and ischemic liver disease.
- Elevated serum alkaline phosphatase and GGT occur in cases of liver injury with a cholestatic pattern and therefore often accompany conditions such as primary biliary cirrhosis, primary sclerosing cholangitis, drug-induced cholestasis, and bile duct obstruction.
- Elevations in serum conjugated (or direct) bilirubin indicate hepatocellular dysfunction or cholestasis. Indirect bilirubin elevations occur due to overproduction (as seen with hemolysis), decreased uptake, or decreased hepatic conjugation of bilirubin. Direct hyperbilirubinemia is the result of liver injury or biliary obstruction and is associated with a number of hepatic diseases including cirrhosis.
- Albumin and coagulation factors are markers of hepatic synthetic activity and are used to estimate hepatocyte function in cirrhosis. Reduction in albumin usually indicates a disease duration of more than 3 weeks, whereas severe liver disease can cause PT elevation in less than 24 hours.
- The Child–Pugh classification system uses a combination of physical and laboratory findings to assess and define the severity of cirrhosis and is a predictor of patient survival, surgical outcome, and risk of variceal bleeding (**Table 21-3**).
- The model for end-stage liver disease score for candidates 18 years and over:

  ✓ When all measured parameters are reported in conventional units: 1.33 (if female) $+ [4.56 \times \log_e(\text{bilirubin})] + [0.82 \times (137 - \text{sodium})] - [0.24 \times (137 - \text{sodium}) \times \log_e(\text{bilirubin})] + [9.09 \times \log_e(\text{INR})] + [11.14 \times \log_e(\text{creatinine})] + [1.85 \times (3.5 - \text{albumin})] - [1.83 \times (3.5 - \text{albumin}) \times \log_e(\text{creatinine})] + 6$

  ✓ When all measured parameters are reported in SI units: or 1.33 (if female) $+ [4.56 \times \log_e(\text{bilirubin}/17.1)] + [0.82 \times (137 - \text{sodium})] - [0.24 \times (137 - \text{sodium}) \times \log_e(\text{bilirubin}/17.1)] + [9.09 \times \log_e(\text{INR})] + [11.14 \times \log_e(\text{creatinine}/88.4)] + [1.85 \times (3.5 - \text{albumin}/10)] - [1.83 \times (3.5 - \text{albumin}/10) \times \log_e(\text{creatinine}/88.4)] + 6$

TABLE 21-3

Criteria and Scoring for the Child–Pugh Grading of Chronic Liver Disease

Score	1	2	3
Total bilirubin (mg/dL)	<2 (34.2 μmol/L)	2–3 (34.2–51.3 μmol/L)	>3 (51.3 μmol/L)
Albumin (g/dL)	>3.5 (35 g/L)	2.8–3.5 (28–35 g/L)	<2.8 (28 g/L)
Ascites	None	Mild	Moderate
Encephalopathy (grade)	None	1 and 2	3 and 4
Prothrombin time (seconds prolonged)	<4	4–6	>6

Grade A, <7 points; grade B, 7–9 points; grade C, 10–15 points.

TREATMENT

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- Goals of Treatment: *Resolution of acute complications* such as tamponade of bleeding and resolution of hemodynamic instability for an episode of acute variceal hemorrhage and *prevention of complications* through lowering of portal pressure with medical therapy using nonselective β-adrenergic blocker therapy and supporting abstinence from alcohol.

GENERAL APPROACH TO TREATMENT

- Approaches to treatment include the following:

  ✓ Identify and eliminate the causes of cirrhosis (eg, alcohol abuse).

  ✓ Assess the risk for variceal bleeding and begin pharmacologic prophylaxis with nonselective β-adrenergic blockers when indicated.

  ✓ Variceal obliteration with endoscopic techniques in conjunction with pharmacologic intervention is the recommended treatment of choice in patients with acute bleeding.

  ✓ Evaluate for clinical signs of ascites and manage with pharmacologic treatment (eg, diuretics) and paracentesis. Spontaneous bacterial peritonitis (SBP) should be carefully monitored in patients with ascites who undergo acute deterioration.

  ✓ HE requires clinical vigilance and treatment with dietary restriction, elimination of CNS depressants, and therapy to lower ammonia levels.

  ✓ Frequent monitoring for signs of hepatorenal syndrome, pulmonary insufficiency, and endocrine dysfunction is necessary.

MANAGEMENT OF PORTAL HYPERTENSION AND VARICEAL BLEEDING

- The management of varices involves three strategies: (1) primary prophylaxis to prevent first bleeding episode, (2) treatment of variceal hemorrhage, and (3) secondary prophylaxis to prevent rebleeding in patients who have already bled.

Primary Prophylaxis

- The mainstay of primary prophylaxis is the use of a nonselective β-adrenergic blocking agent such as **propranolol**, **nadolol,** or **carvedilol** to reduce portal pressure.
- β-Adrenergic blocker therapy is recommended in compensated advanced chronic liver disease (cACLD) with clinically significant portal hypertension (CSPH) to prevent decompensation. The use of β-adrenergic blocker therapy is not recommended in cACLD without CSPH.
- Traditional β-adrenergic blocker therapy in CSPH has been oral propranolol 20–40 mg twice daily or nadolol 20–40 mg once daily, titrated every 2–3 days to a resting heart rate of 55–60 beats/min. However, recent guidelines recommend carvedilol initiated at 6.25 mg daily and then increased to twice daily (or 12.5 mg once daily) after 3 days to a target total daily dose of 12.5 mg. Lower starting doses may be utilized in patients with Child–Turcotte–Pugh class B and C cirrhosis.
- The daily dose of propranolol should not exceed 320 mg for patients without ascites or 160 mg for patients with ascites, and for nadolol 160 mg without and 80 mg with ascites. The maximum daily dose of nadolol should not exceed 160 mg for patients without ascites or 80 mg for those with ascites. Maintain systolic blood pressure above 90 mm Hg. For systolic blood pressure below 90 mm Hg, the target maintenance dose of carvedilol may be decreased from 12.5 to 6.25 mg/day.
- β-Adrenergic blocker therapy should be continued indefinitely.
- Endoscopic vein ligation (EVL) is an alternative to β-adrenergic blockers. If EVL is chosen, it will be performed every 2–4 weeks until the obliteration of varices.

ACUTE VARICEAL HEMORRHAGE

- Evidence-based recommendations for select treatments are presented in **Tables 21-4** and **21-5**.

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- Treatment of acute variceal bleeding includes general stabilizing and assessment measures as well as specific measures to control the acute hemorrhage and prevent complications.
- Initial treatment goals include (1) protection of the airway from aspiration of blood, (2) cardiovascular resuscitation, (3) restrictive transfusion, (4) initiation of vasoactive agents, and (5) initiation of antimicrobial prophylaxis.
- Prompt stabilization of blood volume to maintain hemoglobin of 7 g/dL (70 g/L; 4.34 mmol/L) to 8 g/dL (80 g/L; 4.97 mmol/L) is recommended.
- Combination pharmacologic therapy plus EVL (preferred) is the standard approach to treatment of acute variceal bleeding.
- Vasoactive drug therapy is used to stop or slow bleeding as soon as a diagnosis of variceal bleeding is suspected and is started before endoscopy. Treatment with **octreotide** should be initiated early to control bleeding and facilitate endoscopy. Octreotide is administered as an intravenous (IV) bolus of 50 mcg followed by a continuous infusion of 50 mcg/h. It should be continued for 2–5 days after acute variceal bleeding.
- Prophylactic antibiotic therapy is used to prevent SBP and other infections. For all patients with cirrhosis and acute variceal bleeding, IV ceftriaxone 1 g/24 hours is recommended for 5 days. A 250-mg dose of **erythromycin** intravenously prior to endoscopy may be used to accelerate gastric emptying of clots and improve visibility during the endoscopic procedure.
- EVL (in conjunction with pharmacologic therapy) is the recommended form of endoscopic therapy for acute variceal bleeding.

TABLE 21-4

Evidence-Based Table of Select Treatment Recommendations: Variceal Bleeding in Portal Hypertension

Recommendation
Primary prevention of variceal bleeding
Nonselective β-blocker therapy ([preferably carvedilol 12.5 mg/day] should be considered in patients with cACLD and CSPH)
Treatment of variceal bleeding
Short-term antibiotic prophylaxis should be instituted on admission
Vasoactive drugs should be started as soon as possible, prior to endoscopy, and maintained for up to 5 days
Endoscopy should be performed to diagnose variceal bleeding and treat bleeding with EVL
Endoscopy should be performed within 12 hours of presentation
Unless contraindicated, erythromycin 250 mg IV should be administered 30–120 minutes prior to endoscopy
Secondary prophylaxis of variceal bleeding
Nonselective β-blocker therapy plus EVL is the best therapeutic option for prevention of recurrent variceal bleeding

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TABLE 21-5

Evidence-Based Table of Selected Treatment Recommendations: Ascites and Spontaneous Bacterial Peritonitis

Recommendation
Ascites
Paracentesis should be performed in patients with apparent new-onset ascites
Sodium restriction of <2000 mg/day should be instituted as well as oral diuretic therapy with an aldosterone antagonist or an aldosterone antagonist plus loop diuretic
Diuretic-sensitive patients should be treated with sodium restriction and diuretics rather than serial paracentesis
Refractory ascites
Serial therapeutic paracenteses may be performed
Postparacentesis albumin infusion of 6–8 g/L of fluid removed can be considered if more than 5 L is removed during paracentesis
Treatment of SBP
If ascitic fluid polymorphonuclear leukocytes (PMN) counts are >250 cells/mm^3 (0.25×10^9/L), empiric antibiotic therapy should be instituted
If ascitic fluid PMN leukocyte counts are >250 cells/mm^3 (0.25×10^9/L), and the patient has a serum creatinine >1 mg/dL (88 µmol/L), blood urea nitrogen >30 mg/dL (10.7 mmol/L urea), or total bilirubin over 4 mg/dL (68.4 µmol/L), 1.5 g/kg albumin should be infused within 6 hours of detection and 1 g/kg albumin infusion should also be given on day 3
Prophylaxis against SBP
Short-term antibiotic prophylaxis should be used for 7 days to prevent SBP in cirrhosis patients with gastrointestinal hemorrhage
Patients who survive an episode of SBP should receive long-term prophylaxis with ciprofloxacin
Patients with low-protein ascites (<1.5 g/dL [15 g/L]) plus at least one of the following may also justifiably receive long-term ciprofloxacin as prophylaxis: serum creatinine ≥1.2 mg/dL (106 µmol/L), blood urea nitrogen ≥25 mg/dL (8.9 mmol/L), serum sodium ≤130 mEq/L (mmol/L), or Child–Pugh score of ≥9 with bilirubin ≥3 mg/dL (51.3 µmol/L)

Secondary Prophylaxis Against Recurrent Variceal Hemorrhage

- A nonselective β-adrenergic blocker along with EVL is the best treatment option for variceal bleeding—secondary prophylaxis. Patients should be monitored for evidence of bradycardia, bronchospasm, and hypoglycemia, particularly in patients with insulin-dependent diabetes, as well as symptoms of heart failure and excessive sodium and water retention.

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- Patients who cannot tolerate or who fail pharmacologic and endoscopic interventions can be considered for tips to prevent bleeding.

ASCITES

- For patients with ascites, a serum–ascites albumin gradient should be determined. If the gradient is ≥1.1 g/dL (11 g/L), the patient almost certainly has portal hypertension.
- The primary treatment of ascites secondary to portal hypertension consists of sodium restriction (to less than 2 g/day) and oral diuretic therapy. Fluid loss and weight change depend directly on sodium balance in these patients. A goal of therapy is to produce a weight loss of ascitic fluid of up to 0.5 kg/day, assuming the patient is without other peripheral edema, and increase urinary excretion of sodium to >80 mmol/day.
- Diuretic therapy should be initiated with **spironolactone** 100 mg alone for the first occurrence of ascites titrated every 3 days to a maximum of 400 mg daily. Addition of **furosemide** is recommended in those with insufficient weight loss, hyperkalemia, or long-standing or recurring ascites. Furosemide is initiated at 40 mg daily and is titrated according to response and tolerability to a maximum of 160 mg daily.
- If tense ascites is present, paracentesis should be performed prior to institution of diuretic therapy and salt restriction.
- Patients with intolerable gynecomastia from spironolactone may be transitioned to eplerenone (100-mg spironolactone is equivalent to approximately 50-mg eplerenone) or amiloride (100-mg spironolactone is equivalent to approximately 10-mg amiloride).

SPONTANEOUS BACTERIAL PERITONITIS

- Patients with documented or suspected SBP should receive broad-spectrum antibiotic therapy. Patients with ascitic fluid PMN counts greater than or equal to 250 cells/mm^3 (0.25×10^9/L) should receive empiric antibiotic therapy.
- A third-generation cephalosporin (eg, **cefotaxime** or **ceftriaxone**) is recommended for community-acquired SBP (ie, when diagnosed at the time of admission or within 48 hours of admission) in patients without risk factors for infection with multidrug-resistant organisms (MDROs).
- **Piperacillin/tazobactam** is recommended in patients with risk factors for MDRO infections. Vancomycin should be added in patients with prior infection with, or a positive nasal swab for, methicillin-resistant *Staphylococcus aureus.* **Daptomycin** should be added in patients with prior infection with or positive swab for vancomycin-resistant enterococcus.
- Patients who survive an episode of SBP should receive long-term antibiotic prophylaxis with daily ciprofloxacin 500 mg.

HEPATIC ENCEPHALOPATHY

- The general approach to the management of HE is four pronged and includes the following: care for patients with altered consciousness, identify and treat any other causes besides HE for altered mental status, identify and treat any precipitating factors, and begin empirical HE treatment.
- The grading system for HE is provided in **Table 21-6**.
- Treatment approaches include reduction in blood ammonia concentrations by protein withdrawal, with drug therapy aimed at inhibiting ammonia production or enhancing its removal (nonabsorbable disaccharides such as **lactulose** and antibiotics).
- To reduce blood ammonia concentrations in patients with episodic HE, protein intake is withheld (while maintaining caloric intake) until the clinical situation improves. Once successful reversal of HE symptoms is achieved, protein intake can be titrated back up based on tolerance to a total of 1.2–1.5 g/kg/day. Vegetable-source and dairy-source protein may be preferable to meat-source protein because the latter contains a higher calorie-to-nitrogen ratio.
- In episodic HE, lactulose is initiated at a dose of 30 mL (20 g) orally every 1–2 hours until catharsis begins and the patient experiences one to two bowel movements. The dose is then adjusted to produce two to three soft stools per day for chronic therapy. Patients are monitored for changes to their electrolytes periodically as well as for changes in mental status. Polyethylene glycol 3350 may be considered for patients suffering an acute HE episode.

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- **Rifaximin** 550 mg twice daily plus lactulose is effective in the treatment of HE.
- Other adjunctive therapies include zinc replacement (50 mg/day) in patients with zinc deficiency and flumazenil in cases of refractory HE with the possibility of benzodiazepine use.

TABLE 21-6

Grading System for Hepatic Encephalopathy

Grade	Level of Consciousness	Personality/Intellect	Neurologic Abnormalities
Unimpaired	Normal	Normal	Normal
Minimal	No clinical evidence of change	No clinical evidence of change/alterations identified on psychometric or neuropsychological testing	No clinical evidence of change
I	Trivial lack of awareness; shortened attention span	Euphoria or anxiety; impairment of addition or subtraction	Altered sleep rhythm
II	Lethargic	Obvious personality changes; inappropriate behavior; apathy	Asterixis; dyspraxia; disoriented for time
III	Somnolent but arousable	Bizarre behavior	Responsive to stimuli; confused; gross disorientation to time and space
IV	Coma/unarousable	None	Does not respond to stimuli

EVALUATION OF THERAPEUTIC OUTCOMES

- **Table 21-7** summarizes the drug monitoring guidelines for patients with cirrhosis and portal hypertension, including monitoring parameters and therapeutic outcomes.

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TABLE 21-7

Drug Monitoring Guidelines

Drug	Adverse Drug Reaction	Monitoring Parameter	Comments
Nonselective β-adrenergic blocker	Heart failure, bronchospasm, glucose intolerance	BP, HR Goal HR: 55–60 beats/min or maximal tolerated dose	Nadolol, propranolol
Nonselective β-adrenergic blocker; alpha-blocker	Similar to nonselective β-adrenergic blocker, but potentially better tolerated	Goal BP: Systolic > 90 mm Hg	Carvedilol
Octreotide	Bradycardia, hypertension, arrhythmia, abdominal pain	HR, ECG, abdominal pain	
Spironolactone/furosemide	Electrolyte disturbances, dehydration, renal insufficiency, hypotension	Serum electrolytes (especially potassium), SCr, blood urea nitrogen, BP Goal sodium excretion: >80 mmol/day	Spot urine sodium concentration greater than potassium concentration correlates well with daily sodium excretion >80 mmol/day
Lactulose	Electrolyte disturbances	Serum electrolytes Goal number of soft stools per day: 2–3	
Neomycin	Ototoxicity, nephrotoxicity	SCr, annual auditory monitoring	
Metronidazole	Neurotoxicity	Sensory and motor neuropathy	
Rifaximin	Nausea, diarrhea		

BP, blood pressure; ECG, electrocardiogram; HR, heart rate; SCr, serum creatinine.

See Chapter 58, Portal Hypertension and Cirrhosis, authored by Julie M. Sease for a more detailed discussion of this topic.

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